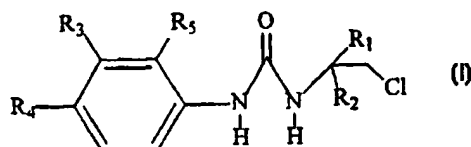




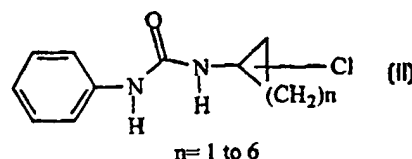
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(21) International Application Number: PCT/CA00/00413 (22) International Filing Date: 12 April 2000 (12.04.00) (30) Priority Data: 2,268,588 12 April 1999 (12.04.99) CA (71) Applicant (for all designated States except US): UNIVERSITE LAVAL [CA/CA]; Pavillon des Sciences de l'Education, local 1442, Cité universitaire, Ste-Foy, Quebec G1K 7P4 (CA). (72) Inventor; and (75) Inventor/Applicant (for US only): GAUDREAU, René, C. [CA/CA]; 2102, Chemin Aubin, St-Nicolas, Quebec G7A 2N3 (CA). (74) Agents: DUBUC, Jean, H. et al.; Goudreau Gage Dubuc, The Stock Exchange Tower, Suite 3400, 800 Place Victoria, Montreal, Quebec H4Z 1E9 (CA).		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	

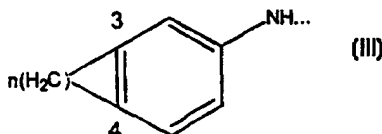
(54) Title: NOVEL ARYL-CHLORO-ETHYL UREAS



(I)



n = 1 to 6



(III)

(57) Abstract

Described herein are novel 1-aryl-3-(2-chloroethyl)ureas derivatives. These derivatives are useful anticancer agents having excellent specificity towards cell targets and potent antineoplastic activity without systemic toxicity or mutagenicity. More specifically, the invention is directed to novel derivatives of formula (I), wherein R₁ is C₁-C₆ lower alkyl, C₃-C₇ cycloalkyl, C₁-C₆ lower alkoxy, C₁-C₆ hydroxy alkyl, or C₁-C₆ lower halide; R₂ is H, C₁-C₆ lower alkyl, C₃-C₇ cycloalkyl, C₁-C₆ lower alkoxy, C₁-C₆ hydroxy alkyl or C₁-C₆ lower halide, di-halide or tri-halide; R₁ and R₂ may also be part of cyclic structures expressed by formula (II), R₃ and R₄ are as defined in R₅ or, halide, di-halide, trihalide, C₁-C₇ lower dialkyl, or alicyclic groups of structure (III), wherein n = 2 to 8 carbon atoms, said alicyclic ring can be substituted by one or more groups as defined in R₅; or polycyclic rings bearing not more than three rings wherein the rings other than the ring bearing the substituted 2-chloroethylamino moiety can be substituted by one or more groups as defined in R₅; R₅ is H, C₁-C₇ lower alkyl, C₁-C₇ lower alkoxy, C₁-C₇ hydroxy alkyl, C₁-C₇ amino alkyl, C₁-C₆ thio alkyl, C₁-C₅ S-lower alkyl, C₁-C₇ N-lower alkyl, C₁-C₇ N,N-dilower alkyl, C₁-C₇ lower cyanoalkyl, C₁-C₇ lower haloalkyl, C₁-C₇ lower sulfoxide or C₃-C₇ cycloalkyl; or a prodrug thereof. Also disclosed are pharmaceutical compositions containing the compounds of the invention in conjunction with a pharmaceutically acceptable carrier and the use of the compositions in treating cancer.

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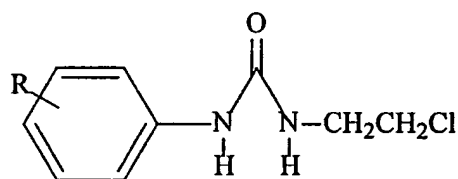
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TITLE OF THE INVENTION: NOVEL ARYL-CHLORO-ETHYL UREAS**BACKGROUND OF THE INVENTION****5 1. Field of Invention**

This invention relates to novel anticancer agents having potent antineoplastic activity without systemic toxicity or mutagenicity. Moreover, the compounds of the present invention present higher specificity to cancer cell targets than previously known compounds. The present invention also relates to
10 pharmaceutical compositions comprising at least one compound of the present invention as active agent. More specifically, the invention is directed to novel derivatives of 1-aryl-3-(2-chloroethyl)ureas having substituents on the first carbon atom of the 2-chloroethyl moiety.

2. The Prior Art

15 Some 1-aryl-3-(2-chloroethyl)urea derivatives (hereinafter referred to as "CEUs") are known from US Patents 5,530,026 and 5,750,547 to the same assignee as the present application. More specifically, compounds of the following formula are known:



wherein R refers to various substituents on the phenyl ring.

20 It is known that CEUs display an affinity towards cancer cells, permeate the cell wall and provide a mild alkylating effect on cell components thereby killing the offending cell.

- 2 -

An object of the invention is to provide novel CEU derivatives having significantly superior antineoplastic activity over known CEUs while maintaining low systemic toxicity, mutagenicity and side-effects.

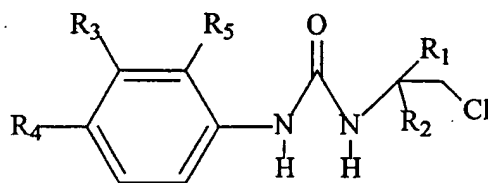
5 SUMMARY OF THE INVENTION

It has now been found, against expectations and documented precedents that specific substitutions on the first carbon atom of the 2-chloroethyl group of the CEU molecule provides a significant improvement on the anticancer effect of the resulting CEU.

- 10 Moreover, it has been found that yet unknown substitutions on the phenyl ring render the resulting CEU molecule even more efficient at targeting specific regions of cancerous cells thereby improving their specificity toward various cellular proteins key to cell survival.

More specifically, this invention provides a novel class of CEU derivatives. This

- 15 novel class of CEU may be expressed by the following formula:



wherein

R_1 is lower alkyl (1 to 6 carbon atoms) or

cycloalkyl (3 to 7 carbon atoms) or

lower alkoxy or hydroxy alkyl (1 to 6 carbon atoms)

- 20 lower halide, lower di-halide or lower tri-halide (Br, I, Cl, F) (1 to 6 carbon atoms)

R_2 is H or

lower alkyl (1 to 6 carbon atoms) or

cycloalkyl (3 to 7 carbon atoms) or

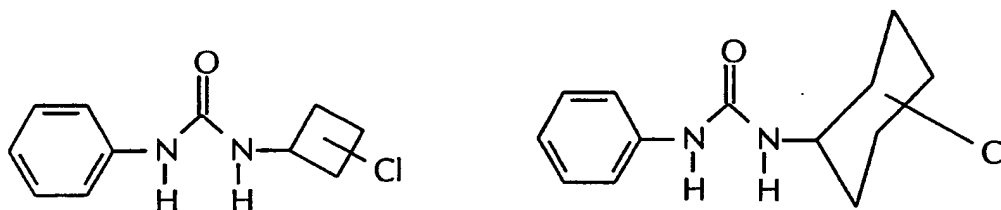
- 25 lower alkoxy or hydroxy alkyl (1 to 6 carbon atoms)

- 3 -

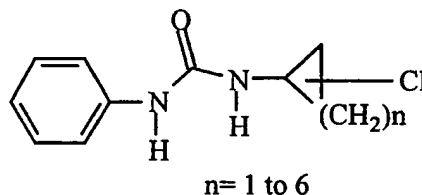
lower halide, lower di-halide or lower tri-halide (Br, I, Cl, F) (1 to 6 carbon atoms)

R_1 and R_2 could also be part of cyclic structures expressed by the formula:

examples:



5

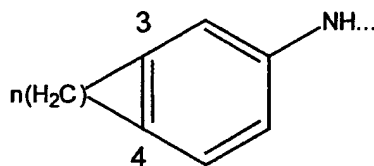


R_3 and R_4 are as defined in R_5 , or halide, dihalide or trihalide (e.g. CF_3)

lower dialkyl (1 to 8 carbon atoms)

in R_3 and R_4 , (the number of carbon atoms present is not necessarily identical ("asymmetric molecules")) or

10 alicyclic groups of the following structures

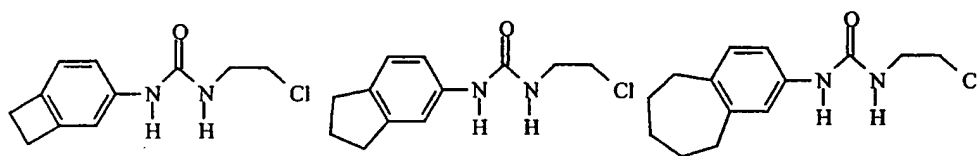


wherein $n = 2$ to 8 carbon atoms,

The alicyclic ring could also be substituted by one or more substituting groups comprising groups as described for R_5

15 R_3 and R_4 can also be polycyclic rings bearing not more than three rings such as dihydrophenanthrene, anthracene, phenanthrene, fluorenyl, etc., examples:

- 4 -



wherein the rings other than the ring bearing the substituted 2-chloroethylamino moiety can be substituted by one or more groups as defined in R_5 .

R_5 is H or

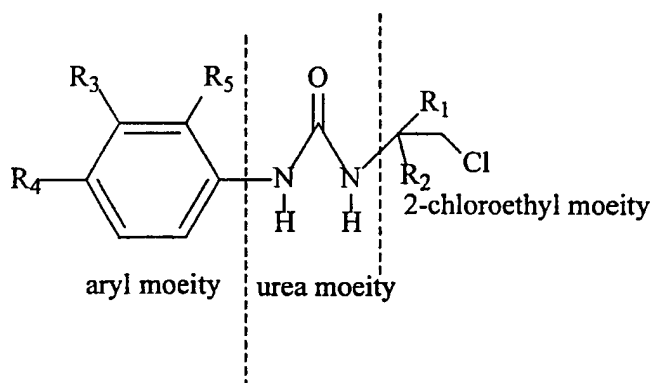
- 5 lower alkyl (1 to 7 carbon atoms) or
lower alkoxy or hydroxy alkyl, amino alkyl, thio alkyl (1 to 7 carbon atoms) or
S-lower alkyl
N-lower alkyl
- 10 N,N-dilower alkyl
lower cyanoalkyl (1 to 7 carbon atoms)
cycloalkyl (3 to 7 carbons atoms)
lower haloalkyls (Br, I, Cl, F) (1 to 7 carbon atoms)
lower sulfoxides (1 to 7 carbon atoms)
- 15 Further scope of applicability of the present invention will become apparent from the detailed description given hereinafter. It should be understood, however, that this detailed description, while indicating preferred embodiments of the invention, is given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent
- 20 to those skilled in the art.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Before describing the present invention in detail, it is to be understood that the invention is not limited in its application to the details of the preferred embodiments and examples described herein. The invention is capable of other
5 embodiments and of being practised in various ways. It is also to be understood that the phraseology or terminology used herein is for the purpose of description and not limitation.

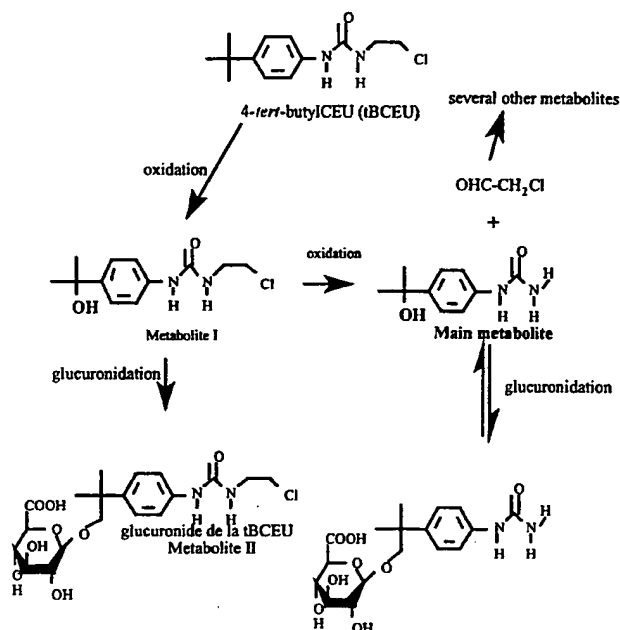
MODIFICATION OF THE 2-CHLOROETHYL MOIETY (R_1 and R_2 groups)

- 10 Experiments to assess the biopharmaceutical properties of known 1-aryl-3-(2-chloroethyl) ureas (CEUs) have unexpectedly revealed that certain cell enzymes such as cytochromes P450 1A2 and 2E1 were oxidizing CEUs therefore metabolizing them to inert molecules and depriving them of anticancer effect. The metabolization mechanism was again unexpectedly found to operate on the
15 first carbon atom on the chloro-2-ethyl moiety adjacent to the urea moiety.



- 6 -

For example, in the case of a 4-*tert*-butyl CEU (tBCEU), metabolization occurred along the following pathway:



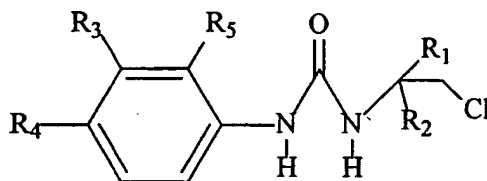
- 5 Surprisingly this has revealed a metabolic weak spot at the first carbon atom of the 2-chloro-ethyl moiety of the CEUs. Thus, the present invention generally aims at providing protecting groups on this first carbon atom and at providing novel CEU derivatives having potent antineoplastic activity.

- 10 More specifically, the protection of the weak carbon atom from metabolization was achieved by substituting the hydrogen atoms with groups such as lower alkyl groups such as methyl, ethyl and propyl.

MODIFICATION OF THE R₃, R₄ AND R₅ MOIETIES

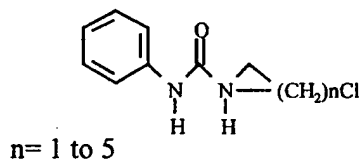
- 15 Furthermore, it was surprisingly discovered that certain modifications of substituents on the aryl moiety dramatically improved the specificity of the resulting CEU derivatives toward various cellular proteins key to cell survival.

Thus, the following compounds were developed and are expressed by the general formula:



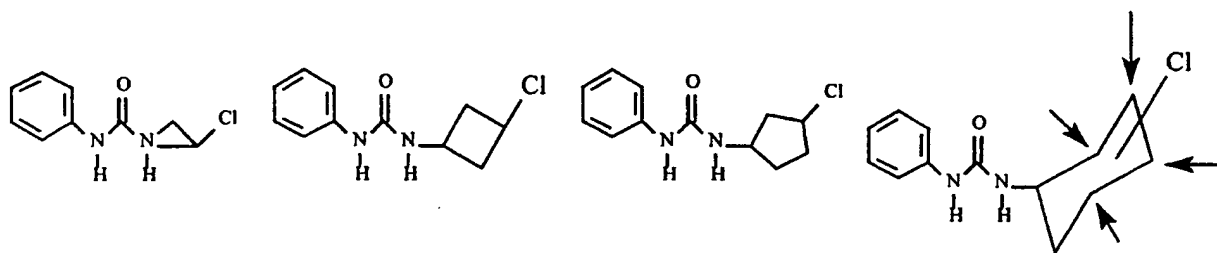
wherein

- 5 **R₁** is lower alkyl (1 to 6 carbon atoms) or
cycloalkyl (3 to 7 carbon atoms) or
lower alkoxy or hydroxy alkyl (1 to 6 carbon atoms)
lower halide, lower di-halide or lower tri-halide (Br, I, Cl, F) (1 to 6
carbon atoms)
- 10 **R₂** is H or
lower alkyl (1 to 6 carbon atoms) or
cycloalkyl (3 to 7 carbon atoms) or
lower alkoxy or hydroxy alkyl (1 to 6 carbon atoms)
lower halide, lower di-halide or lower tri-halide (Br, I, Cl, F) (1 to 6
carbon atoms)
- 15 **R₁** and **R₂** can be part of cyclic structures expressed by the formula:



- 8 -

Such as:



- 10 wherein the arrows on the molecule on the right hand side indicate the position where the molecule can be substituted by the chlorine atom;

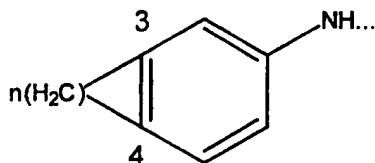
R₃ and R₄ are as defined in R₅ or halide, dihalide or trihalide (e.g. CF₃)

lower dialkyl (1 to 8 carbon atoms)

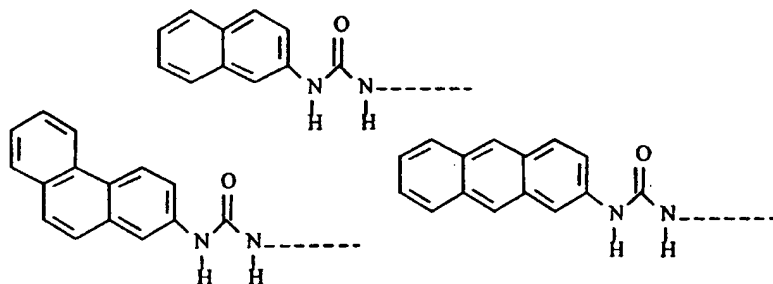
in R₃ and R₄, (the number of carbon atoms present is not necessarily identical

- 15 ("asymmetric molecules")) or

alicyclic groups of the following structures

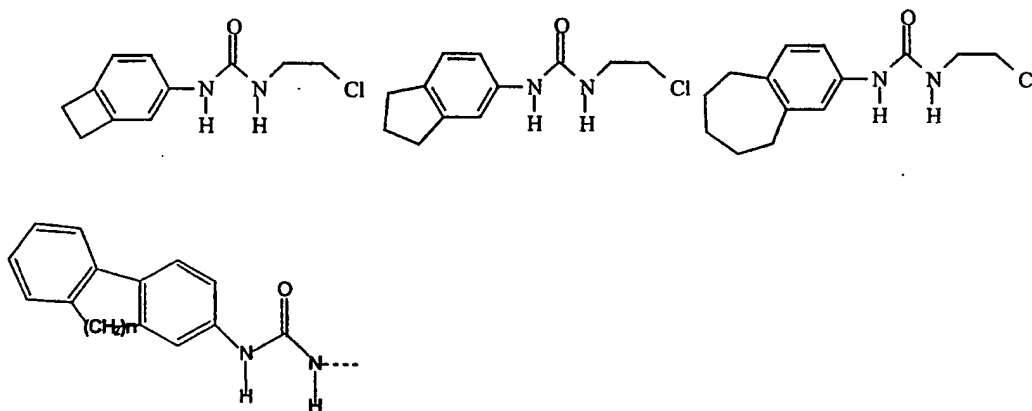


wherein n = 2 to 8 carbon atoms,



- 20 R₃ and R₄ can also be polycyclic rings bearing not more than three rings such as dihydrophenanthrene, dihydroanthracene, anthracene, phenanthrene, fluorenyl, etc., examples:

- 9 -



wherein the rings other than the ring bearing the substituted 2-chloroethylamino moiety can be substituted by one or more groups as defined in R_5 .

- 5 R_5 is H or
 lower alkyl (1 to 7 carbon atoms) or
 lower alkoxy or hydroxy alkyl, amino alkyl, thio alkyl (1 to 7 carbon atoms) or
 S-lower alkyl
 10 N-lower alkyl
 N,N-dilower alkyl
 lower cyanoalkyl (1 to 7 carbon atoms)
 cycloalkyl (3 to 7 carbons atoms)
 lower haloalkyls (Br, I, Cl, F) (1 to 7 carbon atoms)
 15 lower sulfoxides (1 to 7 carbon atoms)

PREPARATION OF CEU DERIVATIVES

The compounds of the present invention are easily prepared in good yields without concomitant polymerization or decomposition. The compounds are also easily purified by usual techniques such as crystallization or liquid
 20 chromatography. Furthermore, the compounds exhibit an extended shelf life without decomposition in air.

- 10 -

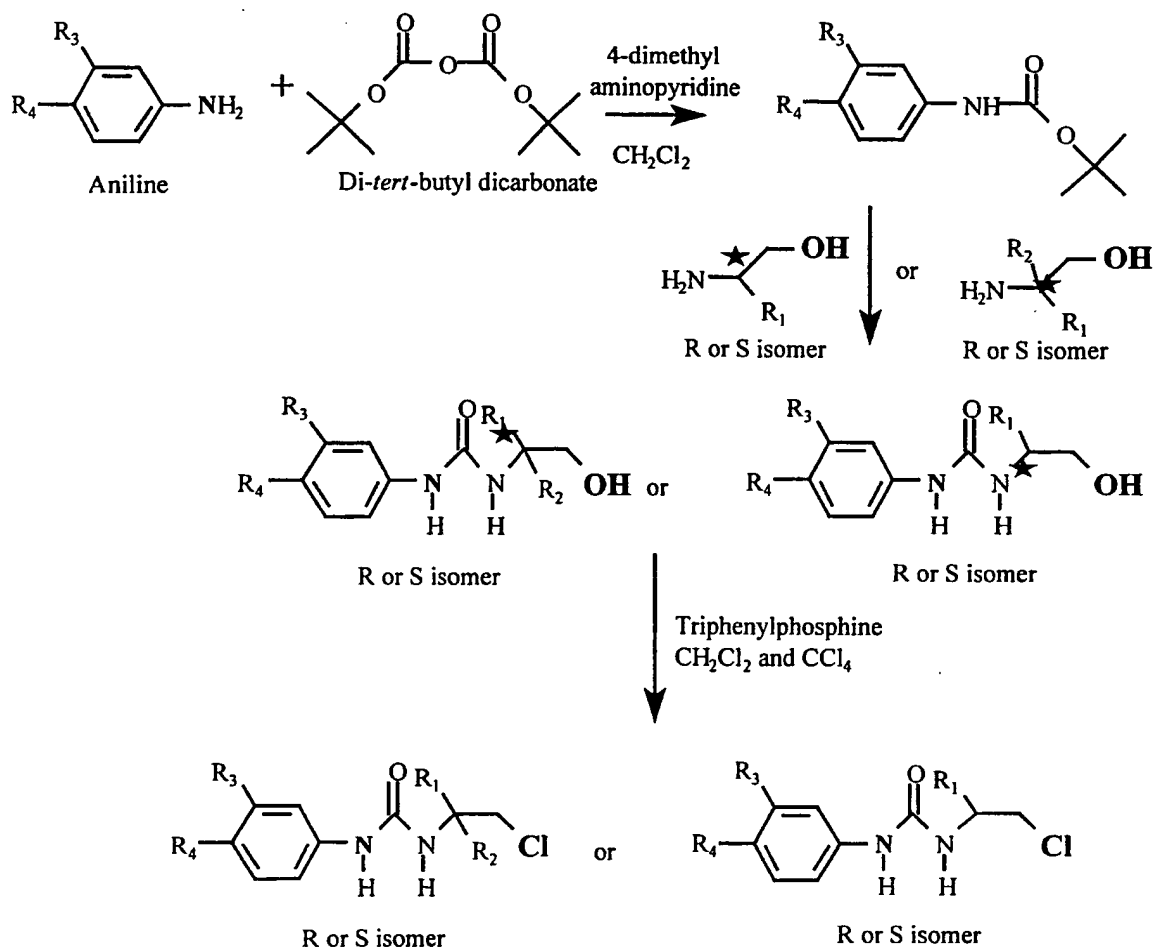
The type and level of activity for a given dosage of each compound can be conventionally determined by routine experimentation using well-known pharmacological protocols.

5 The compounds of the present invention appear to kill cancer tumor cells by alkylation of their β -tubulin on a specific cysteine residue (Cyst-239) and also by other mechanisms under investigation. The molecular structure of β -tubulin has been highly conserved throughout evolution and is therefore present in many mammalian cells. Consequently, the compounds of the invention are indicated for: wideranging anticancer agents, transdermic for pre-surgical treatment of
10 melanomas and systemic for other cancers.

Prodrugs of the compounds of the present invention may also be easily prepared. As an example of prodrugs of the compounds of the present invention, the sulfone and sulfoxide derivatives of alkylthio substituents is immediately contemplated by skilled worker in this art. The sulfone and
15 sulfoxide derivatives while not generally active will be activated once administered to a patient. The activation will occur when the prodrug is reduced to yield the corresponding alkylthio, an active compound.

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The following synthesis flowsheet illustrates one route of preparation of CEU derivatives of the present invention.



- 5 It is important to note that the preparation of CEU derivatives of the present invention has led to the formation of R and S isomers which (in some cases) exhibit significant differences in cytotoxic activities (see Tables I and II below).

EXAMPLESPREPARATION OF *N*-(4-ALKYLPHENYL)-*N'*-(1-ALKYL-2-HYDROXY)ETHYLUREAS

These compounds were prepared following the general synthetic route illustrated above.

- 5 To a stirred solution of di-*tert*-butyldicarbonate (3.9 mmol) and 4-dimethylaminopyridine (0.4 mmol) in anhydrous dichloromethane (20 mL) was added dropwise the relevant aniline (also 2-aminofluorenyl, 2-aminonaphthyl, etc. derivatives) (3.7 mmol). The reaction mixture was stirred for 30 min at room temperature and the required (R) or (S) aminoalcohol was added dropwise. The
- 10 mixture was stirred overnight at room temperature. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography on silica gel (dichloromethane/ethyl acetate, 20/80) to yield the hydroxyurea as a colorless solid.

HALOGENATION OF *N*-(4-ALKYLPHENYL)-*N'*-(1-ALKYL-2-HYDROXY)ETHYLUREAS INTO *N*-(4-ALKYLPHENYL)-*N'*-(1-ALKYL-2-CHLORO)ETHYLUREAS

- 15 (4-ALKYLPHENYL)-*N'*-(1-ALKYL-2-CHLORO)ETHYLUREAS
- A solution of the relevant hydroxyurea (2.4 mmol) and triphenylphosphine (3.7 mmol) in a mixture of dichloromethane and carbon tetrachloride (20 : 6) was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the crude product purified by flash chromatography on
- 20 silica gel (ethylether/petroleum ether, 50/50) to give the chloroethylurea as a white solid.

Of import, the R₁ or/and R₂ substituted CEUs may also be prepared by several synthetic routes. One skilled in the art will quickly appreciate this.

EXAMPLE 1: EVALUATION OF CYTOTOXIC ACTIVITY

- 25 Compounds prepared in accordance with the method outlined above were synthesized and evaluated for cytotoxic activity. The molecular structure of each one of them was verified by IR, NMR and mass spectroscopy.

Table I below, provides the evaluation of the *in-vitro* cytotoxic activities of various compounds prepared in accordance with the synthesis illustrated above and in which R₃ and R₅ were H.

5 The conventional evaluation method proposed by the American National Cancer Institute was used. The method measures effectiveness of an anti-cancer drug based on IC₅₀ which symbolizes the drug concentration in μ M at which the drug achieves the inhibition of proliferation of a given line of cancer cells by a factor of one half when compared to the normal proliferation of the same line of cancer cells in the same growth media

10

Cytotoxicity Assay:

CEU were tested on several cell lines including human non-hormone-dependant breast cancer cells (MDA-MB-231), and mouse leukemia (L1210). MDA-MB-231. These cell lines were obtained from the American Type Culture Collection
15 (Bethesda, MD, USA). Cytotoxicity of CEU derivatives was tested and compared to the effect of chlorambucil and carmustine.

Tumor cells were grown in RPMI-1640 medium supplemented with 10% fetal calf serum, 2 mM glutamine and 64 U/mL of gentamycin. Cells were routinely passaged at 90% confluence.

20 Five thousand cells (100 μ l) were seeded in 96 well's plate and incubated for one day at 37°C under a humidified atmosphere, in presence of 5% CO₂. Subsequently, 100 μ l of fresh medium containing CEU to obtain final concentrations ranging from 1- to 200 μ M were added to the cultures. CEU were dissolved in dimethyl sulfoxide (DMSO; Aldrich Chemicals Company Inc.,
25 Milwaukee, WI) which is maintained at 0.5 % (v/v). Cells were incubated for four to five days in the presence of drugs.

Cell's survival was evaluated by colorimetric assay using MTT, according to a modification of the procedure reported by Carmichael and coll. [Carmichael],

- De Graff WG, Gazdar AF, Minna ID, Mitchell JB (1987) *Cancer Res* 47, 936-942]. Briefly, the culture media was replaced by 50 μ l of a solution containing MTT (1.0 mg/ml in PBS: RPMI-1640, (1: 4)). The MTT is reduced by mitochondrial dehydrogenase to form MTT-formazan. After two hours of incubation at 37°C, the wells were washed with 200 μ l of saline and 100 μ L of DMSO containing 0.5% v/v of a glycine solution 0.1 M at pH 11 (NaOH) were added to dissolve the precipitate. The plates were then shaken for 15 minutes and the absorbance read at 570 nm with a Behring Elisa Procesor II (Behring, Marburg, Germany).
- 10 The evaluation was performed on two typical cancer cell lines namely, L1210 (mouse leukemia cells) and MDA-MB-231(human breast cancer cells). A comparison with conventional anti-cancer drugs chlorambucil and carmustine is provided to illustrate the effectiveness of the compounds of the present invention.

15

TABLE I *IN-VITRO* CYTOTOXIC ACTIVITY

IC ₅₀ L1210 (μ M)	IC ₅₀ MDA-MB- 231 (μ M)	R ₁	R ₂	R ₃	R ₄
1.3	3.1	H	H	H	sec-butyl
2.0	4.5	R-methyl	H	H	sec-butyl
19.6	72.4	H	S-methyl H	H	sec-butyl
17	56	R-ethyl	H	H	sec-butyl
20.7	67	H	S-ethyl	H	sec-butyl
14	32	R and S-propyl	H	H	sec-butyl
15	Nd	Methyl	Methyl	H	sec-butyl
2.6	6.2	H	H	H	tert-butyl
2.3	6.1	R-methyl	H	H	tert-butyl
20	74	H	S-methyl	H	tert-butyl
19	55	R-ethyl	H	H	tert-butyl
16	67	H	S-ethyl	H	tert-butyl

IC ₅₀ L1210 (μ M)	IC ₅₀ MDA-MB- 231 (μ M)	R ₁	R ₂	R ₃	R ₄
23	52	R and S-propyl	H	H	<i>tert</i> -butyl
> 100	> 100	Methyl	Methyl	H	<i>tert</i> -butyl
1.2	2.5	H	H	H	<i>iso</i> -propyl
0.5	1.7	R-methyl	H	H	<i>iso</i> -propyl
29.7	> 100	H	S-methyl	H	<i>iso</i> -propyl
16	49	R-ethyl	H	H	<i>iso</i> -propyl
22	85	H	S-ethyl	H	<i>iso</i> -propyl
8.7	24	R and S-propyl	H	H	<i>iso</i> -propyl
80	> 100	Methyl	Methyl	H	<i>iso</i> -propyl
4.5	6.8	Carmustine			
2.6	81	Chlorambucil			

The above experiments show that the R isomer on the R₁ group provided greater activity than the S isomer.

EXAMPLE 2

- 5 In a related set of experiments, the *tert*-butyl group of R₄ was replaced with iodine to yield 4-iodoCEUs (bioisosteric form of the *tert*-butyl group). R₅ remained H. Table II below evaluates the cytotoxicity of such molecules and the effect of substitution on the 2-chloroethylamino moiety. During the experiments, IC₅₀ was recorded against cancer cell lines L1210 and K562 (mouse
- 10 leukemia cells).

TABLE II *IN-VITRO* CYTOTOXIC ACTIVITY

IC ₅₀ L1210 (μ M)	IC ₅₀ K562 (μ M)	R ₁	R ₂	R ₃	R ₄
5.4	3.8	H	H	H	I
1.6	1.1	R-methyl	H	H	I
10	7	H	S-methyl	H	I

This shows that the R isomer of the 4-iodoCEUs (bioisosteric form of the *tert*-butyl group) following a substitution on the 2-chloroethylamino moiety results in a very active drug.

5 EXAMPLE 3

In another related set of experiments wherein R_1 is H or CH_3 , and R_2 is CH_3 , the effect on substitutions on the phenyl ring were observed. It is theorized that theses substitutions assist in the positioning and selectivity of the compounds towards key intracellular proteins.

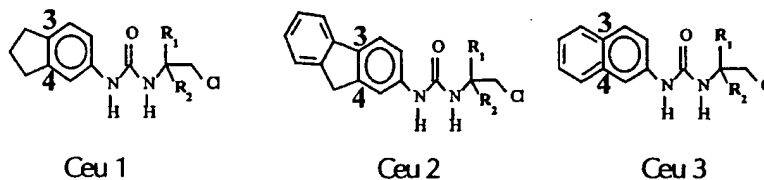
10 The results of *in-vitro* tests are reported in Table III below.

TABLE III *IN-VITRO* CYTOTOXIC ACTIVITY

R_3	R_4	R_5	$\text{IC}_{50} (\mu\text{M})$ (MDA-MB-231)	$\text{IC}_{50} (\mu\text{M})$ L1210
H	Methyl	H	24.1	16.4
Methyl	H	H	60	27
Methyl	Methyl	H	7.2	3.8
Methyl	H	Methyl	20	8.8

From these observations, the R and S alkyl CEU deriving from 3,4 dimethylCEUs
15 are particularly effective anti-cancer agents.

EXAMPLE 4



In another experiment the following polycyclic molecules were prepared:
20 wherein R_1 is H or CH_3 , and R_2 is CH_3 .

In-vitro cytotoxic activities are reported in Table IV below.

TABLE IV *IN-VITRO* CYTOTOXIC ACTIVITY

DRUG	R ₁	R ₂	IC ₅₀ (μM) CHO	IC ₅₀ (μM) MDA-MB-231
CEU-1	H	H	9.9	10.3
CEU-1	R-methyl	H	9.8	9.5
CEU-1		S-methyl	78	> 100
CEU-2	H	H	9.3	9.0
CEU-2	R-methyl	H	16.3	13
CEU-2	H	S-methyl	16.1	50
CEU-3	H	H	7.2	6.1
CEU-3	R-methyl	H	3.1	3.2
CEU-3	H	S-methyl	63	> 100

These results show that the modification of the carbon 1' of CEU led to R and S isomers of CEU. R isomers are in most cases more cytotoxic than the unsubstituted CEU. Furthermore, R isomers are in most cases several fold more potent than the S isomers. This might be due to better specificity toward the protein(s) they alkylate.

EXAMPLE 5

10 The following compounds were successfully tested for cytotoxic activity.

R ₁	R ₂	R ₃	IC ₅₀ (μM) CHO	IC ₅₀ (μM) HT-29	IC ₅₀ (μM) K562	IC ₅₀ (μM) MDA-MB-231
H	R-ethyl	tert-butyl	44	25	32.2	55
H	R-ethyl	iso-propyl	48	30	18	49
H	R-ethyl	sec-butyl	38	27	23	56
H	R-propyl	tert-butyl	60	27	21	52
H	R-propyl	iso-propyl	21.3	17	6	24
H	R-propyl	sec-butyl	29	16.4	11	32

CHO = Chinese Hamster Ovary

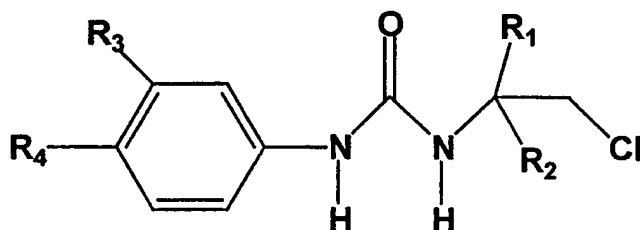
- 18 -

MDA-MB-231 Hormone-independent breast cancer

HT-29 human colon carcinoma

K562 human leukemia

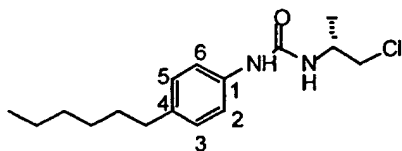
5 EXAMPLES 6-15



Based on the formula of the compounds of the present invention as shown
 10 above, specific molecules were synthesized and later tested for citotoxic activity.

EXAMPLE 6

R ₁	R ₂	R ₃	R ₄
H	Methyl (S configuration)	H	n-hexyl



15 Flash chromatography : ether : petrol ether = 1 : 1

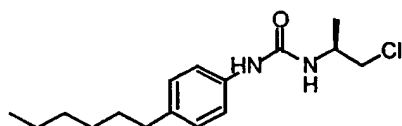
R_f = 0.31 (ether : petrol ether = 1 : 1)

¹H-NMR (CDCl₃) : 7.17 (d, 2H, H-C2 and H-C6, J = 8.4 Hz), 7.11 (d, 2H, H-C3 and H-C5, J = 8.4 Hz), 4.27 (m, 1H, CH(CH₃)CH₂Cl), 3.72 (dd, 1H, CH₂Cl, J = 4.3 and J = 11.0 Hz), 3.57 (dd, 1H, CH₂Cl, J = 3.4 and J = 11.0 Hz), 2.55 (t, 2H, CH₃(CH₂)₄CH₂), 1.53 (m, 2H, CH₃(CH₂)₃CH₂CH₂), 1.23 (d, 3H, CH(CH₃)CH₂Cl, J = 6.9 Hz), 1.18-1.43 (m, 6H, CH₃(CH₂)₃CH₂CH₂), 0.87 (t, 3H, CH₃(CH₂)₅).

20

EXAMPLE 7

R ₁	R ₂	R ₃	R ₄
H	Methyl(Rconfiguration)	H	n-hexyl



5 Flash chromatography : ether : petrol ether = 2 : 3

R_f = 0.29 (ether : petrol ether = 2 : 3)

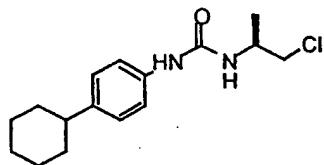
¹H-NMR (CDCl₃) : 7.16 (d, 2H, H-C2 and H-C6, J = 8.5 Hz), 7.07 (d, 2H, H-C3 and H-C5, J = 8.5 Hz), 5.33 (br s, 1H, NH), 4.23 (m, 1H, CH(CH₃)CH₂Cl), 3.65 (dd, 1H, CH₂Cl, J = 4.5 and J = 11.0 Hz), 3.53 (dd, 1H, CH₂Cl, J = 3.5 and J = 11.0 Hz), 2.52 (t, 2H, CH₃(CH₂)₄CH₂, J = 7.5 Hz), 1.50-1.60 (m, 2H, CH₃(CH₂)₃CH₂CH₂), 1.28 (m, 6H, CH₃(CH₂)₃CH₂CH₂), 1.19 (d, 3H, CH(CH₃)CH₂Cl, J = 6.7 Hz), 0.87 (t, 3H, CH₃(CH₂)₅, J = 6.5 Hz).

10

EXAMPLE 8

R ₁	R ₂	R ₃	R ₄
H	Methyl (R configuration)	H	Cyclohexyl

15



Flash chromatography : ether : petrol ether = 1 : 1

¹H-NMR (CDCl₃) : 7.16 (d, 2H, H-C2 and H-C6, J = 8.4 Hz), 7.11 (d, 2H, H-C3 and H-C5, J = 8.4 Hz), 4.24 (m, 1H, CH(CH₃)CH₂Cl), 3.66 (dd, 1H, CH₂Cl, J = 4.2 and J = 11.0 Hz), 3.54 (dd, 1H, CH₂Cl, J = 3.4 and J = 11.0 Hz), 2.43 (m,

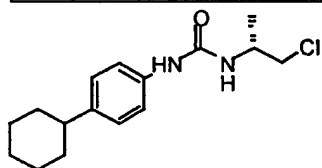
20

- 20 -

1H, CH-Ph), 1.70-1.90 (m, 6H, H-cyclohexyl), 1.35-1.45 (m, 4H, H-cyclohexyl), 1.20 (d, 3H, CH(CH₃)CH₂Cl, J = 6.7 Hz).

EXAMPLE 9

R ₁	R ₂	R ₃	R ₄
H	Methyl (S configuration)	H	cyclohexyl



5

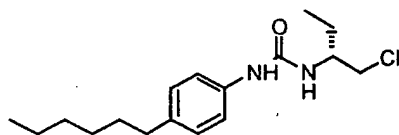
Flash chromatography : ether : petrol ether = 1 : 1

R_f = 0.24 (ether : petrol ether = 1 : 1)

¹H-NMR (CDCl₃): 7.18 (d, 2H, H-C2 and H-C6, J = 8.7 Hz), 7.14 (d, 2H, H-C3 and H-C5, J = 8.7 Hz), 4.27 (m, 1H, CH(CH₃)CH₂Cl), 3.71 (dd, 1H, CH₂Cl, J = 4.4 and J = 11.0 Hz), 3.56 (dd, 1H, CH₂Cl, J = 3.2 and J = 11.0 Hz), 2.45 (m, 1H, CH-Ph), 1.70-1.85 (m, 6H, H-cyclohexyl), 1.36 (m, 4H, H-cyclohexyl), 1.23 (d, 3H, CH(CH₃)CH₂Cl, J = 6.8 Hz).

15 **EXAMPLE 10**

R ₁	R ₂	R ₃	R ₄
H	-ethyl (R configuration)	H	n-hexyl



Flash chromatography : ether : petrol ether = 10 : 11

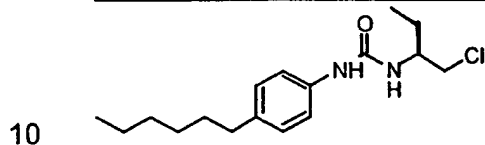
- 21 -

$R_f = 0.38$ (ether : petrol ether = 1 : 1)

$^1\text{H-NMR}$ (CDCl_3): 7.17 (d, 2H, H-C2 and H-C6, $J = 8.4$ Hz), 7.08 (d, 2H, H-C3 and H-C5, $J = 8.4$ Hz), 5.24 (br s, 1H, NH), 4.02 (m, 1H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 3.69 (dd, 1H, CH_2Cl , $J = 4.0$ and 11.0 Hz), 3.60 (dd, 1H, CH_2Cl , $J = 3.3$ and 11.0 Hz), 2.53 (t, 2H, CH_2Ph , $J = 7.8$ Hz), 1.56 (m, 4H, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{CH}_2$ and $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 1.28 (m, 6H, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{CH}_2$), 0.89 (2t, 6H, $\text{CH}_3(\text{CH}_2)_5$ and $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 6.5$ and 7.4 Hz).

EXAMPLE 11

R_1	R_2	R_3	R_4
H	-ethyl (R configuration)	H	n-hexyl



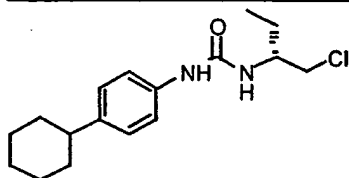
Flash chromatography : ether : petrol ether = 35 : 65

$R_f = 0.28$ (ether : petrol ether = 2 : 3)

$^1\text{H-NMR}$ (CDCl_3): 7.16 (d, 2H, H-C2 and H-C6, $J = 8.2$ Hz), 7.06 (d, 2H, H-C3 and H-C5, $J = 8.2$ Hz), 5.41 (br s, 1H, NH), 4.02 (m, 1H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 3.67 (dd, 1H, CH_2Cl , $J = 4.2$ and 11.0 Hz), 3.58 (dd, 1H, CH_2Cl , $J = 3.5$ and 11.0 Hz), 2.52 (t, 2H, CH_2Ph , $J = 7.7$ Hz), 1.55 (m, 4H, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{CH}_2$ and $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 1.28 (m, 6H, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{CH}_2$), 0.89 (2t, 6H, $\text{CH}_3(\text{CH}_2)_5$ and $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 6.6$ and 7.5 Hz).

EXAMPLE 12

R ₁	R ₂	R ₃	R ₄
H	Ethyl (S configuration)	H	cyclohexyl



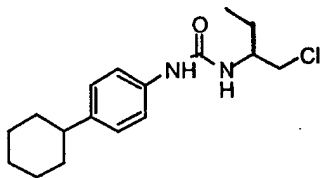
Flash chromatography : ether : petrol ether = 10 : 11

5 R_f = 0.38 (ether : petrol ether = 1 : 1)

¹H-NMR (CDCl₃) : 7.18 (d, 2H, H-C2 and H-C6, J = 8.7 Hz), 7.14 (d, 2H, H-C3 and H-C5, J = 8.7 Hz), 4.04 (m, 1H, CH(CH₃)CH₂Cl), 3.73 (dd, 1H, CH₂Cl, J = 4.0 and J = 11.2 Hz), 3.63 (dd, 1H, CH₂Cl, J = 3.2 and J = 11.2 Hz), 2.46 (m, 1H, CH-Ph), 1.70-1.85 (m, 4H, H-cyclohexyl), 1.58 (m, 2H, CH(CH₂CH₃)CH₂Cl),
 10 1.18-1.45 (m, 6H, H-cyclohexyl), 0.93 (t, 3H, CH(CH₂CH₃)CH₂Cl, J = 7.4 Hz).

EXAMPLE 13

R ₁	R ₂	R ₃	R ₄
H	Ethyl (R configuration)	H	cyclohexyl



15

Flash chromatography : ether : petrol ether = 1 : 1

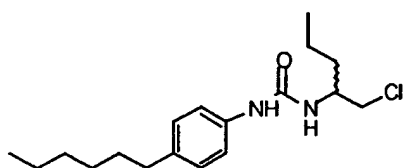
R_f = 0.35 (ether : petrol ether = 1 : 1)

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- $^1\text{H-NMR}$ (CDCl_3) : 7.18 (d, 2H, H-C2 and C6, $J = 8.5$ Hz), 7.13 (d, 2H, H-C3 and H-C5, $J = 8.5$ Hz), 4.03 (m, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$), 3.72 (dd, 1H, CH_2Cl , $J = 3.9$ and $J = 11.1$ Hz), 3.64 (dd, 1H, CH_2Cl , $J = 3.4$ and $J = 11.1$ Hz), 2.45 (m, 1H, CH-Ph), 1.65-1.95 (m, 4H, H-cyclohexyl), 1.56 (m, 2H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$),
 5 1.20-1.40 (m, 6H, H-cyclohexyl), 0.93 (t, 3H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 7.4$ Hz).

EXAMPLE 14

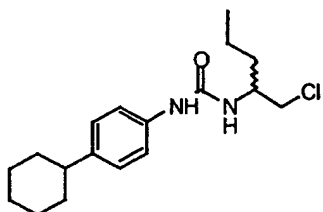
R_1	R_2	R_3	R_4
H	Propyl (mixture of R and S isomers)	H	n-hexyl



- 10 Flash chromatography : ether : petrol ether = 2 : 3
 $R_f = 0.31$ (ether : petrol ether = 2 : 3)
 $^1\text{H-NMR}$ (CDCl_3) : 7.17 (d, 2H, H-C2 et C6, $J = 8.2$ Hz), 7.04 (d, 2H, H-C3 et C5, $J = 8.2$ Hz), 4.05 (m, 1H, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 3.64 (dd, 1H, CH_2Cl , $J = 4.3$ et $J = 11$ Hz), 3.54 (dd, 1H, CH_2Cl , $J = 3.7$ et $J = 11$ Hz), 2.51 (t, 2H, $\text{CH}_3(\text{CH}_2)_4\text{CH}_2$, $J = 7.7$ Hz), 1.25-1.60 (m, 12H, $\text{CH}_3(\text{CH}_2)_4\text{CH}_2$ and $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 0.88 (t, 3H, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 7.2$ Hz).
 15

EXAMPLE 15

R ₁	R ₂	R ₃	R ₄
H	Propyl (mixture of R and S isomers)	H	cyclohexyl



¹H-NMR (CDCl₃) : 7.18 (d, 2H, H-C2 et C6, J = 8.7 Hz), 7.13 (d, 2H, H-C3 et C5, J = 8.7 Hz), 4.13 (m, 1H, CH(CH₂CH₂CH₃)CH₂Cl), 3.73 (dd, 1H, CH₂Cl, J = 4.1 et J = 11.1 Hz), 3.59 (dd, 1H, CH₂Cl, J = 3.5 et J = 11.1 Hz), 2.45 (m, 1H, CH-Ph), 1.20-2.00 (m, 14H, CH₂-cyclohexyl et CH(CH₂CH₂CH₃)CH₂Cl), 0.91 (t, 3H, CH(CH₂CH₂CH₃)CH₂Cl, J = 7.1 Hz).

10 EXAMPLE 16: EVALUATION OF CYTOTOXICITY ACTIVITY:

Cell culture. Tumor cell lines (B16-F0, Caco-2, DU-145, HT-29, MDA-MB-231 and other cell lines described so far in the patent application) were obtained from the American Type Culture Collection (ATCC HTB-26; Bethesda, MD). Cells were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum (Hyclone, Road Logan, Utah) and were cultured in a humidified atmosphere at 37 °C in 5% CO₂.

Drugs: All drugs were dissolved in DMSO and the final concentration of DMSO in the culture medium was maintained at 0.5 % (v/v).

Cytotoxicity assays. At day-1, tumor cells in suspension in 100 μ l were plated in microtiter plates (96 wells). On day-0, tumor cells were treated by addition of escalating concentrations of the drug (100 μ l solution). On that day, the number of living cells was determined in wells that were untreated. This was performed in order to be able to evaluate the toxic concentration of the drug needed to kill

- 25 -

50% of the cellular population present at the beginning of the experiments. This value is represented by C_{50} in the table. At day-3, the number of living cells is determined using either MTT or resazurin assays. Growth inhibition activity of these compounds was expressed as the concentration of CEU inhibiting cell growth by 50% G_{50} in the following table

The MTT assay was as described above in Example 1. The Resazurin assay was performed as follows:

Aspirate the supernatant (cell suspension: centrifuge first)

Add 100 μ L NaCl 0.9% (saline)

10 Aspirate the supernatant (cell suspension: centrifuge first)

Add 50 μ L RZ (resazurin 125 μ g/ml/PBS : RPMI without FBS ; 1 : 4)

Incubate at 37°C

Collect fluorescence data at different time.

	FILTER	EM	EM
15	CENTER	590	590

TABLE V *IN-VITRO* CYTOTOXIC ACTIVITY

Cell line	R ₁	R ₂	R ₃	R ₄	C ₅₀ (μ M)	G ₅₀ (μ M)	C ₅₀ /G ₅₀
HT-29	H	Methyl (R isomer)	H	n-hexyl	12.8	5.1	2.51
DU-145	idem	idem	Idem	Idem	11.8	6.3	1.86
MDA-MB-231	idem	idem	Idem	Idem	31.9	11.7	2.72
Caco-2	idem	idem	Idem	Idem	21.1	12.6	1.68
B16-F0	idem	idem	idem	Idem	18.2	16.3	1.12
DU-145	H	Methyl (S isomer)	H	n-hexyl	39.5	18.9	2.09
B16-F0	idem	idem	idem	Idem	31.3	26.3	1.19
MDA-MB-231	idem	idem	idem	Idem	43.3	31.5	1.37
HT-29	idem	idem	idem	Idem	44.5	32.3	1.38
Caco-2	idem	idem	idem	Idem	44.2	35.8	1.23
HT-29	H	propyl (racemic)	H	n-hexyl	20.3	10.7	1.90

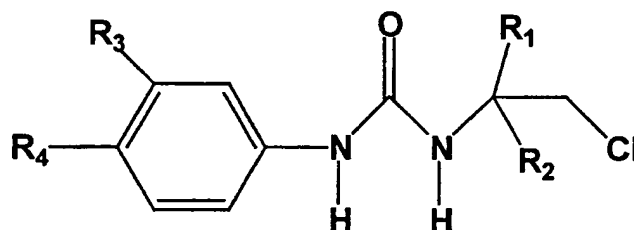
Cell line	R ₁	R ₂	R ₃	R ₄	C ₅₀ (μM)	G ₅₀ (μM)	C ₅₀ /G ₅₀
		mixture)					
DU-145	idem	idem	idem	Idem	19.6	10.9	1.80
Caco-2	idem	idem	idem	Idem	21.1	12.7	1.34
B16-F0	idem	idem	idem	Idem	21.3	15.8	1.71
MDA-MB-231	idem	idem	idem	Idem	32.3	18.9	1.71
DU-145	H	ethyl (S isomer)	H	n-hexyl	27.2	7.4	3.68
Caco-2	idem	idem	idem	Idem	13.7	10.2	1.35
MDA-MB-231	idem	idem	idem	Idem	40.6	18	
B16-F0	idem	idem	idem	Idem	24.9	18.8	1.33
HT-29	idem	idem	idem	Idem	36.8	20.8	1.77
DU-145	H	ethyl (R isomer)	H	n-hexyl	15.8	4.6	3.46
Caco-2	idem	idem	idem	idem	10.9	7.5	1.45
HT-29	idem	idem	idem	idem	20.8	13.1	1.58
B16-F0	idem	idem	idem	idem	18.3	14.1	1.29
MDA-MB-231	idem	idem	idem	idem	30.1	15.1	1.99
DU-145	H	methyl (S isomer)	H	cyclohexyl	27.6	7.8	3.52
Caco-2	idem	idem	idem	idem	14.7	8.6	1.70
B16-Fo	idem	idem	idem	idem	17.4	15.4	1.13
HT-29	idem	idem	idem	idem	28.1	19	1.48
MDA-MB-231	idem	idem	idem	idem	42.9	27.5	1.56
DU-145	H	methyl (R isomer)	H	cyclohexyl	25.2	8.6	2.94
Caco-2	idem	idem	idem	idem	20.3	15.4	1.32
HT-29	idem	idem	idem	idem	23.9	17.1	1.40
B16-F0	idem	idem	idem	idem	22.1	21.8	1.01
MDA-MB-231	idem	idem	idem	idem	42.3	27.6	1.53
DU-145	H	ethyl (S isomer)	H	cyclohexyl	22.2	7.3	3.04
Caco-2	idem	idem	idem	idem	17.7	10	1.77
HT-29	idem	idem	idem	idem	22.8	13.6	1.68
B16-F0	idem	idem	idem	idem	21.5	17.3	1.24
MDA-MB-231	idem	idem	idem	idem	40.3	19.6	2.05

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Cell line	R ₁	R ₂	R ₃	R ₄	C ₅₀ (μM)	G ₅₀ (μM)	C ₅₀ /G ₅₀
DU-145	H	ethyl (R isomer)	H	cyclohexyl	16.2	6.9	2.35
HT-29	idem	idem	idem	idem	16.3	9.8	2.35
Caco-2	idem	idem	idem	idem	15.6	9.9	1.57
B16-F0	idem	idem	idem	idem	17.7	15.5	1.14
MDA-MB-231	idem	idem	idem	idem	32.5	16.3	1.99

EXAMPLES 17-29

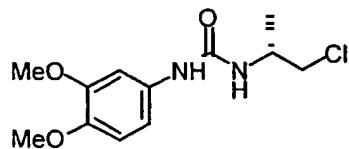
5



Based on the formula of the compounds of the present invention as shown above, specific molecules were synthesized and later tested for citotoxic activity.

10 EXAMPLE 17

R1	R2	R3	R4
H	Methyl (R-isomer)	Methoxy	Methoxy



Flash chromatography : 9 / 1 : ether / petrol ether

15 R_f = 0.31 (100% ether)

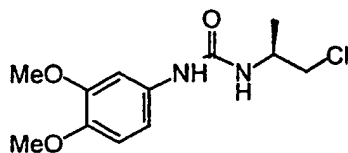
- 28 -

$^1\text{H-NMR}$ (CDCl_3): 6.95 (d, 1H, H-C2, $J = 2.2$ Hz), 6.72 (d, 1H, H-C5, $J = 8.4$ Hz), 6.64 (dd, 1H, H-C6, $J = 2.0$ and $J = 8.4$ Hz), 4.21 (m, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$), 3.78 (s, 6H, 2 OCH_3), 3.67 (dd, 1H, CH_2Cl , $J = 4.1$ and $J = 10.9$ Hz), 3.50 (dd, 1H, CH_2Cl , $J = 3.3$ and $J = 10.9$ Hz), 1.17 (t, 3H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 6.7$ Hz).

5

EXAMPLE 18

R1	R2	R3	R4
H	Methyl (S-isomer)	Methoxy	Methoxy



10 Flash chromatography : 9 / 1 : ether / petrol ether

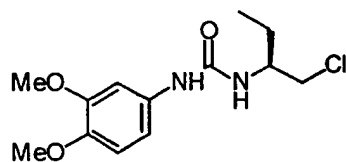
$R_f = 0.33$ (100% ether)

$^1\text{H-NMR}$ (CDCl_3): 6.96 (d, 1H, H-C2, $J = 2$ Hz), 6.70 (d, 1H, H-C5, $J = 8.5$ Hz), 6.63 (d, 1H, H-C6, $J = 8.5$ Hz), 4.20 (m, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$), 3.76 et 3.78 (2s, 6H, 2 OCH_3), 3.65 (dd, 1H, CH_2Cl , $J = 4.2$ and $J = 11.0$ Hz), 3.49 (dd, 1H,

15 CH_2Cl , $J = 3.4$ and $J = 11.0$ Hz), 1.16 (t, 3H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 6.8$ Hz).

EXAMPLE 19

R1	R2	R3	R4
H	Ethyl (S-isomer)	Methoxy	Methoxy



5 Flash chromatography :7 / 3 : ether / petrol ether

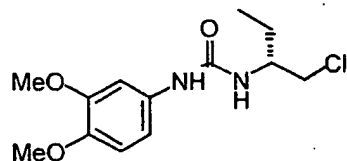
$R_f = 0.17$ (7 / 3 : ether / petrol ether)

$^1\text{H-NMR}$ (CDCl_3): 6.99 (d, 1H, H-C2, $J = 2.3$ Hz), 6.80 (d, 1H, H-C5, $J = 8.4$ Hz), 6.72 (d, 1H, H-C6, $J = 8.4$ Hz), 4.04 (m, 1H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 3.85 (s, 6H, 2 OCH_3), 3.75 (dd, 1H, CH_2Cl , $J = 3.9$ and $J = 11.2$ Hz), 3.63 (dd, 1H,

10 CH_2Cl , $J = 3.3$ and $J = 11.2$ Hz), 1.57 (m, 2H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 0.93 (t, 3H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 7.5$ Hz).

EXAMPLE 20

R1	R2	R3	R4
H	Ethyl (R-isomer)	Methoxy	Methoxy



15

Flash chromatography :7 / 3 : ether / petrol ether

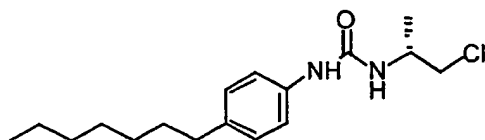
$R_f = 0.17$ (7 / 3 : ether / petrol ether)

- 30 -

- ¹H-NMR (CDCl₃): 7.02 (d, 1H, H-C2, J = 2.2 Hz), 6.77 (d, 1H, H-C5, J = 8.7 Hz), 6.70 (dd, 1H, H-C6, J = 2.2 and J = 8.7 Hz), 4.03 (m, 1H, CH(CH₂CH₃)CH₂Cl), 3.83 (s, 6H, 2 OCH₃), 3.73 (dd, 1H, CH₂Cl, J = 4.0 and J = 11.2 Hz), 3.61 (dd, 1H, CH₂Cl, J = 3.2 and J = 11.2 Hz), 1.56 (m, 2H, CH(CH₂CH₃)CH₂Cl), 0.92 (t, 3H, CH(CH₂CH₃)CH₂Cl, J = 7.4 Hz).

EXAMPLE 21

R1	R2	R3	R4
H	Methyl (R-isomer)	H	n-heptyl



10

Flash chromatography : 35 / 65 : ether / petrol ether

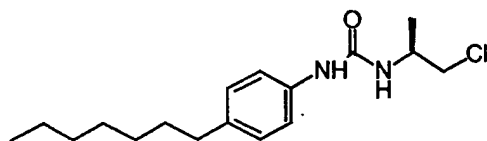
 $R_f = 0.16$ (2 / 3 : ether / petrol ether)

- ¹H-NMR (CDCl₃): 7.15 (d, 2H, H-C2 and H-C6, J = 8.4 Hz), 7.07 (d, 2H, H-C3 and H-C5, J = 8.4 Hz), 4.25 (m, 1H, CH(CH₃)CH₂Cl), 3.65 (dd, 1H, CH(CH₃)CH₂Cl, J = 4.5 and J = 11.0 Hz), 3.53 (dd, 1H, CH(CH₃)CH₂Cl, J = 3.6 and J = 11.0 Hz), 2.53 (t, 2H, CH₃(CH₂)₅CH₂, J = 7.8 Hz), 1.55 (m, 2H, CH₃(CH₂)₄CH₂CH₂), 1.28 (m, 8H, CH₃(CH₂)₄CH₂CH₂), 1.20 (d, 3H, CH(CH₃)CH₂Cl, J = 6.7 Hz), 0.87 (t, 3H, CH₃(CH₂)₆, J = 6.8 Hz).

EXAMPLE 22

R1	R2	R3	R4
H	Methyl (S-isomer)	H	n-heptyl

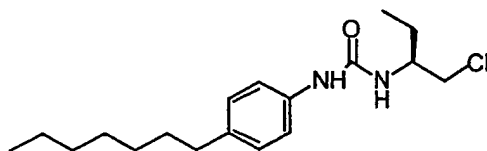
- 31 -

Flash chromatography : 4 / 5 / 1 : CH₂Cl₂ / petrol ether / ether $R_f = 0.23$ (2 / 3 : ether / petrol ether)

- 5 ¹H-NMR (CDCl₃): 7.16 (d, 2H, H-C2 and H-C6, J = 8.3 Hz), 7.07 (d, 2H, H-C3 and H-C5, J = 8.3 Hz), 4.23 (m, 1H, CH(CH₃)CH₂Cl), 3.65 (dd, 1H, CH(CH₃)CH₂Cl, J = 4.5 and J = 11.0 Hz), 3.53 (dd, 1H, CH(CH₃)CH₂Cl, J = 3.5 and J = 11.0 Hz), 2.52 (t, 2H, CH₃(CH₂)₅CH₂, J = 7.7 Hz), 1.55 (m, 2H, CH₃(CH₂)₄CH₂CH₂), 1.28 (m, 8H, CH₃(CH₂)₄CH₂CH₂), 1.19 (d, 3H, CH(CH₃)CH₂Cl, J = 6.6 Hz), 0.87 (t, 3H, CH₃(CH₂)₆, J = 6.6 Hz).
- 10

EXAMPLE 23

R1	R2	R3	R4
H	Ethyl (S-isomer)	H	n-heptyl



15

Flash chromatography : 4 / 5 / 1 : CH₂Cl₂ / petrol ether / ether $R_f = 0.31$ (2 / 3 : ether / petrol ether)

- ¹H-NMR (CDCl₃): 7.17 (d, 2H, H-C2 and H-C6, J = 8.2 Hz), 7.09 (d, 2H, H-C3 and H-C5, J = 8.2 Hz), 4.03 (m, 1H, CH(CH₂CH₃)CH₂Cl), 3.70 (dd, 1H, CH(CH₂CH₃)CH₂Cl, J = 3.7 and J = 11.0 Hz), 3.61 (dd, 1H, CH(CH₂CH₃)CH₂Cl, J = 3.2 and J = 11.0 Hz), 2.53 (t, 2H, CH₃(CH₂)₅CH₂, J = 7.7 Hz), 1.57 (m, 4H, CH₃(CH₂)₄CH₂CH₂ and CH(CH₂CH₃)CH₂Cl), 1.27 (m, 8H, CH₃(CH₂)₄CH₂CH₂),
- 20

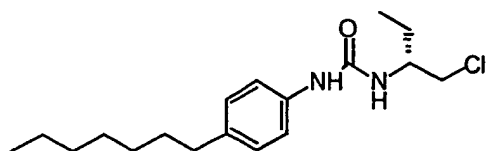
- 32 -

0.92 and 0.87 (2t, 6H, $\text{CH}_3(\text{CH}_2)_6$ and $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 7.6$ and $J = 7.0$ Hz).

EXAMPLE 24

R1	R2	R3	R4
H	Ethyl (R-isomer)	H	n-heptyl

5



Flash chromatography : 4 / 5 / 1 : CH_2Cl_2 / petrol ether / ether

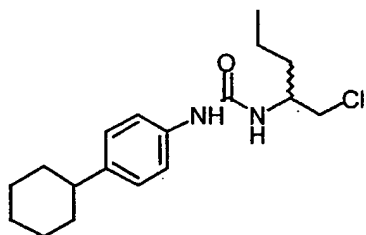
$R_f = 0.31$ (2 / 3 : ether / petrol ether)

- 10 $^1\text{H-NMR}$ (CDCl_3) : 7.16 (d, 2H, H-C2 and H-C6 $J = 8.5$ Hz), 7.06 (d, 2H, H-C3 and H-C5, $J = 8.5$ Hz), 4.00 (m, 1H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 3.67 (dd, 1H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 4.2$ and $J = 11.1$ Hz), 3.58 (dd, 1H, $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 3.5$ and $J = 11.1$ Hz), 2.53 (t, 2H, $\text{CH}_3(\text{CH}_2)_5\text{CH}_2$, $J = 7.7$ Hz), 1.54 (m, 4H, $\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{CH}_2$ and $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 1.28 (m, 8H, $\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{CH}_2$),
- 15 0.91 and 0.87 (2t, 6H, $\text{CH}_3(\text{CH}_2)_6$ and $\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 7.4$ and $J = 7.1$ Hz).

EXAMPLE 25

R1	R2	R3	R4
H	Propyl (racemic mixture)	H	cyclohexyl

- 33 -



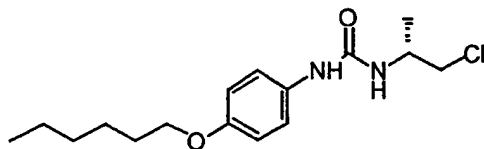
Flash chromatography : 2 / 3 : ether / petrol ether

 $R_f = 0.31$ (2 / 3 : ether / petrol ether)

- 5 $^1\text{H-NMR}$ (CDCl_3): 7.16 (d, 2H, H-C2 and H-C6, $J = 8.6$ Hz), 7.08 (d, 2H, H-C3 and H-C5, $J = 8.6$ Hz), 4.08 (m, 1H, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$), 3.66 (dd, 1H, CH_2Cl , $J = 4.2$ and $J = 11.0$ Hz), 3.55 (dd, 1H, CH_2Cl , $J = 3.6$ and $J = 11.0$ Hz), 2.42 (m, 1H, CH-Ph), 1.70-1.82 (m, 6H, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$ and H-cyclohexyl), 1.20-1.60 (m, 8H, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$ and H-cyclohexyl), 0.88 (t, 3H, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 7.2$ Hz).
- 10

EXAMPLE 26

R1	R2	R3	R4
H	Methyl (R-isomer)	H	n-hexyloxy



15

Flash chromatography : 1 / 1 : ether / petrol ether

 $R_f = 0.16$ (1 / 1 : ether / petrol ether)

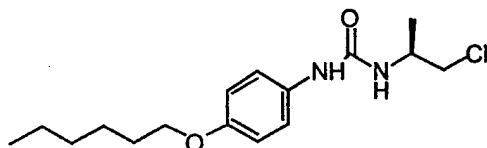
- $^1\text{H-NMR}$ (CDCl_3): 7.16 (d, 2H, H-C2 and H-C6, $J = 8.7$ Hz), 6.85 (d, 2H, H-C3 and H-C5, $J = 8.7$ Hz), 4.26 (m, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$), 3.92 (t, 2H, $\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{O}$, $J = 6.6$ Hz), 3.72 (dd, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 4.3$ and $J = 11.0$ Hz), 3.55 (dd, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 3.5$ and $J = 11.0$ Hz), 1.76 (m, 2H,
- 20

$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{CH}_2\text{O}$), 1.24-1.50 (m, 6H, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{CH}_2\text{O}$), 1.21 (d, 3H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 6.7 \text{ Hz}$), 0.90 (t, 3H, $\text{CH}_3(\text{CH}_2)_5\text{O}$, $J = 6.9 \text{ Hz}$).

EXAMPLE 27

R1	R2	R3	R4
H	Methyl (S-isomer)	H	n-hexyloxy

5



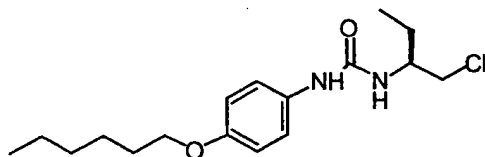
Flash chromatography : 55 / 35 / 10 : CH_2Cl_2 / petrol ether / ether

$R_f = 0.16$ (1 / 1 : ether / petrol ether)

- 10 $^1\text{H-NMR}$ (CDCl_3) : 7.13 (d, 2H, H-C2 and H-C6, $J = 7.7 \text{ Hz}$), 6.79 (d, 2H, H-C3 and H-C5, $J = 7.7 \text{ Hz}$), 4.21 (m, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$), 3.87 (t, 2H, $\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{O}$, $J = 6.5 \text{ Hz}$), 3.64 (dd, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 4.5$ and $J = 11.0 \text{ Hz}$), 3.52 (dd, 1H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 3.5$ and $J = 11.0 \text{ Hz}$), 1.74 (m, 2H, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{CH}_2\text{O}$), 1.24-1.45 (m, 6H, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{CH}_2\text{O}$), 1.18 (d, 3H, $\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$, $J = 6.6 \text{ Hz}$), 0.89 (m, 3H, $\text{CH}_3(\text{CH}_2)_5\text{O}$).
- 15

EXAMPLE 28

R1	R2	R3	R4
H	Ethyl (S-isomer)	H	n-hexyloxy



- 35 -

Flash chromatography : 55 / 35 / 10 : CH₂Cl₂ / petrol ether / ether

R_f = 0.26 (1 / 1 : ether / petrol ether)

¹H-NMR (CDCl₃) : 7.16 (d, 2H, H-C2 and C6, J = 8.8 Hz), 6.82 (d, 2H, H-C3 and C5, J = 8.8 Hz), 4.01 (m, 1H, CH(CH₃)CH₂Cl), 3.90 (t, 2H, CH₃(CH₂)₄CH₂O, J = 6.6 Hz), 3.70 (dd, 1H, CH(CH₂CH₃)CH₂Cl, J = 4.0 and J = 11.2 Hz), 3.60 (dd, 1H, CH(CH₂CH₃)CH₂Cl, J = 3.3 and J = 11.2 Hz), 1.75 (m, 2H, CH₃(CH₂)₃CH₂CH₂O), 1.20-1.70 (m, 8H, CH₃(CH₂)₃CH₂CH₂O) and CH(CH₂CH₃)CH₂Cl, 0.90 (2t, 6H, CH₃(CH₂)₅O and CH(CH₂CH₃)CH₂Cl, J = 7.4 and J = 6.5 Hz).

10

EXAMPLE 29: EVALUATION OF CYTOTOXICITY ACTIVITY:

Cell culture. Tumor cell lines (B16-F0, Caco-2, DU-145, HT-29, MDA-MB-231 and other cell lines described so far in the patent application) were obtained from the American Type Culture Collection (ATCC HTB-26; Bethesda, MD).

15 Cells were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum (Hyclone, Road Logan, Utah) and were cultured in a humidified atmosphere at 37 °C in 5% CO₂.

Drugs: All drugs were dissolved in DMSO and the final concentration of DMSO in the culture medium was maintained at 0.5 % (v/v).

20 Cytotoxicity assays. At day-1, tumor cells in suspension in 100 μl were plated in microtiter plates (96 wells). On day-0, tumor cells were treated by addition of escalating concentrations of the drug (100 μl solution). On that day, the number of living cells was determined in wells that were untreated. The number of living cells is determined using either MTT or resazurin assays. Growth inhibition
25 activity of these compounds was expressed as the concentration of CEU inhibiting cell growth by 50% G₅₀ in the following table

The MTT assay was as described above in Example 1. The Resazurin assay was performed as follows:

- 36 -

Aspirate the supernatant (cell suspension: centrifuge first)

Add 100 μ L NaCl 0.9% (saline)

Aspirate the supernatant (cell suspension: centrifuge first)

Add 50 μ L RZ (resazurin 125 μ g/ml/PBS : RPMI without FBS ; 1 : 4)

5 Incubate at 37°C

Collect fluorescence data at different time.

FILTER	EM	EM
CENTER	590	590

10

TABLE VI *IN-VITRO* CYTOTOXIC ACTIVITY

Cell line	R1	R2	R3	R4	G50 (μ M)
B16-F0	H	Ethyl (R-isomer)	H	n-Heptyl	3,74
Caco-2	H	Ethyl (R-isomer)	H	n-Heptyl	4,85
CHO	H	Ethyl (R-isomer)	H	n-Heptyl	3,14
DU-145	H	Ethyl (R-isomer)	H	n-Heptyl	4,02
HT-29	H	Ethyl (R-isomer)	H	n-Heptyl	2,94
K562	H	Ethyl (R-isomer)	H	n-Heptyl	2,90
L1210	H	Ethyl (R-isomer)	H	n-Heptyl	4,04
MCF-7	H	Ethyl (R-isomer)	H	n-Heptyl	3,78
MDA-MB-231	H	Ethyl (R-isomer)	H	n-Heptyl	5,17
T24	H	Ethyl (R-isomer)	H	n-Heptyl	3,61
B16-F0	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
Caco-2	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
CHO	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
DU-145	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
HT-29	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
K562	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
L1210	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
MCF-7	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
MDA-MB-231	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
T24	H	Ethyl (R-isomer)	Methoxy	Methoxy	> 100
B16-F0	H	Ethyl (S-isomer)	H	n-Heptyl	4,77
Caco-2	H	Ethyl (S-isomer)	H	n-Heptyl	6,32
CHO	H	Ethyl (S-isomer)	H	n-Heptyl	4,20
DU-145	H	Ethyl (S-isomer)	H	n-Heptyl	4,89
HT-29	H	Ethyl (S-isomer)	H	n-Heptyl	5,01

Cell line	R1	R2	R3	R4	G50 (μ M)
K562	H	Ethyl (S-isomer)	H	n-Heptyl	3,59
L1210	H	Ethyl (S-isomer)	H	n-Heptyl	5,67
MCF-7	H	Ethyl (S-isomer)	H	n-Heptyl	4,20
MDA-MB-231	H	Ethyl (S-isomer)	H	n-Heptyl	6,12
T24	H	Ethyl (S-isomer)	H	n-Heptyl	3,93
B16-F0	H	Ethyl (S-isomer)	H	n-Hexyloxy	8,26
Caco-2	H	Ethyl (S-isomer)	H	n-Hexyloxy	9,50
CHO	H	Ethyl (S-isomer)	H	n-Hexyloxy	3,28
DU-145	H	Ethyl (S-isomer)	H	n-Hexyloxy	9,46
HT-29	H	Ethyl (S-isomer)	H	n-Hexyloxy	8,12
K562	H	Ethyl (S-isomer)	H	n-Hexyloxy	3,88
L1210	H	Ethyl (S-isomer)	H	n-Hexyloxy	7,42
MCF-7	H	Ethyl (S-isomer)	H	n-Hexyloxy	10,41
MDA-MB-231	H	Ethyl (S-isomer)	H	n-Hexyloxy	8,75
T24	H	Ethyl (S-isomer)	H	n-Hexyloxy	7,16
B16-F0	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
Caco-2	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
CHO	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
DU-145	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
HT-29	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
K562	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
L1210	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
MCF-7	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
MDA-MB-231	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
T24	H	Ethyl (S-isomer)	Methoxy	Methoxy	> 100
B16-F0	H	H	H	Cyclohexyl	7,77
Caco-2	H	H	H	Cyclohexyl	9,37
CHO	H	H	H	Cyclohexyl	6,16
DU-145	H	H	H	Cyclohexyl	9,09
HT-29	H	H	H	Cyclohexyl	8,78
K562	H	H	H	Cyclohexyl	7,12
L1210	H	H	H	Cyclohexyl	6,94
MCF-7	H	H	H	Cyclohexyl	10,73
MDA-MB-231	H	H	H	Cyclohexyl	9,17
T24	H	H	H	Cyclohexyl	7,57
B16-F0	H	H	H	n-Heptyl	5,37
Caco-2	H	H	H	n-Heptyl	8,07
CHO	H	H	H	n-Heptyl	5,39

Cell line	R1	R2	R3	R4	G50 (μ M)
DU-145	H	H	H	n-Heptyl	7,16
HT-29	H	H	H	n-Heptyl	4,90
K562	H	H	H	n-Heptyl	3,85
L1210	H	H	H	n-Heptyl	4,59
MCF-7	H	H	H	n-Heptyl	8,62
MDA-MB-231	H	H	H	n-Heptyl	7,87
T24	H	H	H	n-Heptyl	3,41
B16-F0	H	H	H	n-Hexyloxy	5,38
Caco-2	H	H	H	n-Hexyloxy	8,42
CHO	H	H	H	n-Hexyloxy	5,35
DU-145	H	H	H	n-Hexyloxy	12,41
HT-29	H	H	H	n-Hexyloxy	6,95
K562	H	H	H	n-Hexyloxy	5,13
L1210	H	H	H	n-Hexyloxy	5,99
MCF-7	H	H	H	n-Hexyloxy	9,88
MDA-MB-231	H	H	H	n-Hexyloxy	10,18
T24	H	H	H	n-Hexyloxy	4,28
B16-F0	H	H	Methoxy	Methoxy	35,33
Caco-2	H	H	Methoxy	Methoxy	> 100
CHO	H	H	Methoxy	Methoxy	33,05
DU-145	H	H	Methoxy	Methoxy	48,22
HT-29	H	H	Methoxy	Methoxy	18,98
K562	H	H	Methoxy	Methoxy	5,14
L1210	H	H	Methoxy	Methoxy	19,82
MCF-7	H	H	Methoxy	Methoxy	48,97
MDA-MB-231	H	H	Methoxy	Methoxy	> 100
T24	H	H	Methoxy	Methoxy	20,59
B16-F0	H	Methyl (R-isomer)	H	n-Heptyl	3,79
Caco-2	H	Methyl (R-isomer)	H	n-Heptyl	4,94
CHO	H	Methyl (R-isomer)	H	n-Heptyl	3,46
DU-145	H	Methyl (R-isomer)	H	n-Heptyl	3,63
HT-29	H	Methyl (R-isomer)	H	n-Heptyl	2,17
K562	H	Methyl (R-isomer)	H	n-Heptyl	2,41
L1210	H	Methyl (R-isomer)	H	n-Heptyl	2,42
MCF-7	H	Methyl (R-isomer)	H	n-Heptyl	3,31
MDA-MB-231	H	Methyl (R-isomer)	H	n-Heptyl	4,64
T24	H	Methyl (R-isomer)	H	n-Heptyl	2,18
B16-F0	H	Methyl (R-isomer)	H	n-Hexyloxy	6,38

Cell line	R1	R2	R3	R4	G50 (μ M)
Caco-2	H	Methyl (R-isomer)	H	n-Hexyloxy	8,57
CHO	H	Methyl (R-isomer)	H	n-Hexyloxy	2,63
DU-145	H	Methyl (R-isomer)	H	n-Hexyloxy	13,24
HT-29	H	Methyl (R-isomer)	H	n-Hexyloxy	9,55
K562	H	Methyl (R-isomer)	H	n-Hexyloxy	2,68
L1210	H	Methyl (R-isomer)	H	n-Hexyloxy	6,21
MCF-7	H	Methyl (R-isomer)	H	n-Hexyloxy	8,30
MDA-MB-231	H	Methyl (R-isomer)	H	n-Hexyloxy	10,48
T24	H	Methyl (R-isomer)	H	n-Hexyloxy	7,14
B16-F0	H	Methyl (R-isomer)	Methoxy	Methoxy	26,44
Caco-2	H	Methyl (R-isomer)	Methoxy	Methoxy	> 100
CHO	H	Methyl (R-isomer)	Methoxy	Methoxy	32,16
DU-145	H	Methyl (R-isomer)	Methoxy	Methoxy	34,92
HT-29	H	Methyl (R-isomer)	Methoxy	Methoxy	14,76
K562	H	Methyl (R-isomer)	Methoxy	Methoxy	9,62
L1210	H	Methyl (R-isomer)	Methoxy	Methoxy	10,34
MCF-7	H	Methyl (R-isomer)	Methoxy	Methoxy	25,13
MDA-MB-231	H	Methyl (R-isomer)	Methoxy	Methoxy	43,58
T24	H	Methyl (R-isomer)	Methoxy	Methoxy	12,37
B16-F0	H	Methyl (S-isomer)	H	n-Heptyl	6,60
Caco-2	H	Methyl (S-isomer)	H	n-Heptyl	7,61
CHO	H	Methyl (S-isomer)	H	n-Heptyl	3,80
DU-145	H	Methyl (S-isomer)	H	n-Heptyl	7,46
HT-29	H	Methyl (S-isomer)	H	n-Heptyl	7,69
K562	H	Methyl (S-isomer)	H	n-Heptyl	6,96
L1210	H	Methyl (S-isomer)	H	n-Heptyl	7,48
MCF-7	H	Methyl (S-isomer)	H	n-Heptyl	5,56
MDA-MB-231	H	Methyl (S-isomer)	H	n-Heptyl	8,33
T24	H	Methyl (S-isomer)	H	n-Heptyl	6,15
B16-F0	H	Methyl (S-isomer)	H	n-Hexyloxy	8,45
Caco-2	H	Methyl (S-isomer)	H	n-Hexyloxy	7,98
CHO	H	Methyl (S-isomer)	H	n-Hexyloxy	3,66
DU-145	H	Methyl (S-isomer)	H	n-Hexyloxy	12,55
HT-29	H	Methyl (S-isomer)	H	n-Hexyloxy	10,50
K562	H	Methyl (S-isomer)	H	n-Hexyloxy	7,48
L1210	H	Methyl (S-isomer)	H	n-Hexyloxy	8,20
MCF-7	H	Methyl (S-isomer)	H	n-Hexyloxy	7,99
MDA-MB-231	H	Methyl (S-isomer)	H	n-Hexyloxy	9,08

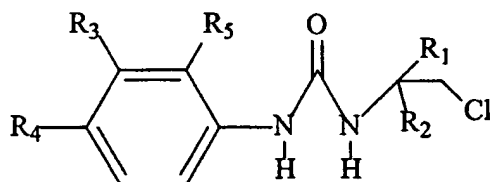
Cell line	R1	R2	R3	R4	G50 (μ M)
T24	H	Methyl (S-isomer)	H	n-Hexyloxy	9,93
B16-F0	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
Caco-2	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
CHO	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
DU-145	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
HT-29	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
K562	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
L1210	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
MCF-7	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
MDA-MB-231	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
T24	H	Methyl (S-isomer)	Methoxy	Methoxy	> 100
B16-F0	H	Propyl (racemic mixture)	H	Cyclohexyl	4,14
Caco-2	H	Propyl (racemic mixture)	H	Cyclohexyl	6,04
CHO	H	Propyl (racemic mixture)	H	Cyclohexyl	2,12
DU-145	H	Propyl (racemic mixture)	H	Cyclohexyl	4,30
HT-29	H	Propyl (racemic mixture)	H	Cyclohexyl	3,03
K562	H	Propyl (racemic mixture)	H	Cyclohexyl	4,93
L1210	H	Propyl (racemic mixture)	H	Cyclohexyl	4,12
MCF-7	H	Propyl (racemic mixture)	H	Cyclohexyl	5,05
MDA-MB-231	H	Propyl (racemic mixture)	H	Cyclohexyl	6,37
T24	H	Propyl (racemic mixture)	H	Cyclohexyl	4,24

Although the invention has been described above with respect with one specific form, it will be evident to a person skilled in the art that it may be modified and refined in various ways. It is therefore wished to have it understood that the present invention should not be limited in scope, except by the terms of the following claims.

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I claim:

1. A compound of formula:

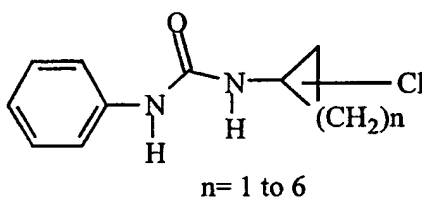


wherein

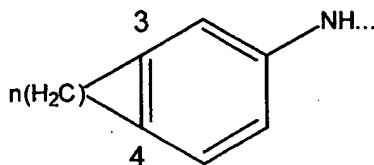
R_1 is C_1 - C_6 lower alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 lower alkoxy, C_1 - C_6 hydroxy alkyl, or C_1 - C_6 lower halide;

R_2 is H, C_1 - C_6 lower alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 lower alkoxy, C_1 - C_6 hydroxy alkyl or C_1 - C_6 lower halide, di-halide or tri-halide;

R_1 and R_2 may also be part of cyclic structures expressed by the formula:



R_3 and R_4 are as defined in R_5 or halide, di-halide, trihalide, C_1 - C_7 lower dialkyl, or alicyclic groups of the following structure



wherein $n = 2$ to 8 carbon atoms, said alicyclic ring can be substituted by one or more groups as defined in R_5 ;

or polycyclic rings bearing not more than three rings wherein the rings other than the ring bearing the substituted 2-chloroethylamino moiety can be substituted by one or more groups as defined in R_5 ;

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R₅ is H, C₁-C₇ lower alkyl, C₁-C₇ lower alkoxy, C₁-C₇ hydroxy alkyl, C₁-C₇ amino alkyl, C₁-C₆ thio alkyl, C₁-C₅ S-lower alkyl, C₁-C₇ N-lower alkyl, C₁-C₇ N,N-dilower alkyl, C₁-C₇ lower cyanoalkyl, C₁-C₇ lower haloalkyl, C₁-C₇ lower sulfoxide or C₃-C₇ cycloalkyl;
or a prodrug thereof.

2. A compound of claim 1 wherein R₂ is R-ethyl or R-propyl.
3. A compound of claim 2 wherein R₄ is Iodine.
4. A compound of claim 2 wherein R₅ is selected from secbutyl, tertbutyl and isopropyl.
5. A compound of claim 1 wherein R₃ and R₄ are methyl.
6. A compound of any of claims 1 to 5 wherein the compound is essentially pure R-isomer form.
7. A pharmaceutical composition comprising the compound of any of claims 1 to 6 and a pharmaceutically acceptable carrier.
8. A medicament for use in treating cancer comprising the compound of any of claims 1 to 6 and a pharmaceutically acceptable carrier.
9. The use of the compound of any of claims 1 to 6 for the treatment of cancer.